REMARKS

Applicants thank Examiners Pak and Eyler for their time to conduct telephone interviews on August 15, 2002, September 18, 2002, and October 10, 2002. The Restriction Requirement dated December 3, 2001 (hereinafter "the Restriction Requirement") and the Office Action dated May 21, 2002 were discussed during the various interviews. Applicants appreciate the Examiners' time and guidance as to what would be required to overcome the rejections of record. While the Examiners made no promises, applicants understood that upon amending the claims and presenting the remarks discussed during the interviews, the claims would be in condition for allowance. Such action is respectfully requested. Should the present submission be non-persuasive in any way, the Examiners are kindly asked to telephone the undersigned.

Claims 40 to 43 and 52 to 73 are now pending in the application. As discussed during the interview, applicants now respectfully traverse the Restriction Requirement, and applicants' reasons for traversal are presented below. Claim 40 has been amended to include the terms "purified polypeptide" and "recombinant polypeptide," which are supported in the specification at page 41, lines 1 to 2, and at page 38, lines 5 to 11, respectively. Claims 43 and 57 were amended to clarify language used in these claims. New claims 72 and 73 have been added. Support for these new claims can be found throughout the specification, e.g., at page 36, line 18 to page 37, line 4, and at page 5, line 20 to page 6, line 11, respectively. The amendments and new claim add no new matter to the present application.

I. The Invention

Applicants were the first to obtain and sequence cDNA encoding a parathyroid hormone (PTH) receptor. Four different PTH receptors from three species (human, rat and opossum) were cloned by applicants and are disclosed in the present application. The present claims are drawn to methods for identifying a compound that inhibits (e.g., by competitive or non-competitive inhibition) binding of PTH to PTH receptors. These methods make use of PTH receptor polypeptides, or fragments thereof, to identify such compounds.

II. Restriction

Applicants confirm their election of Group VI, made on February 4, 2002, and have canceled claims 44 to 51 (Groups II and III) without prejudice as directed to non-elected inventions. However, as discussed during the interview, applicants now traverse the Restriction Requirement with respect to the remaining claims and restriction groups for the reasons discussed below.

Applicants respectfully submit that independent claims 40, 58, and 71 should be examined together because all of these claims relate to methods of identifying compounds that inhibit binding of PTH to PTH receptors. During a telephone interview on August 15, 2002, Examiner Pak indicated that claim 40 (directed to methods of identifying compounds that compete with PTH for binding PTH receptors) was restricted into groups separate from claims 58 and 71 (directed to methods of identifying compounds that inhibit binding of PTH to PTH receptor) because it is not clear that claim 40 is a subgenus of claims 58 and 71. The Examiner suggested that claim 40 be amended to clarify the relationship among these claims, and indicated that if the Examiner approves of the amendment, applicants would be entitled to examination of claims 40, 58, and 71 in the present application. Accordingly, claim 40 has been amended to recite a method for identifying a compound that inhibits binding of PTH to a PTH receptor by competitively binding to the PTH receptor. The amended language of claim 40 clearly indicates that claim 40 is a subgenus of claims 58 and 71. Applicants assume that upon the Examiner's approval of the amendment to claim 40, the following Groups will automatically be recombined: Group I with Group VII, Group IV with Group VIII, Group V with Group IX, and Group VI with Group X. Applicants respectfully request this action.

Further, applicants submit that all remaining restriction groups (Groups I and IV to X) should be recombined into a single group. The relationship between claims 40, 58 and 71 has been addressed above. The present Restriction Requirement also divides the claims into groups based on the use of specific PTH receptors, e.g., opossum (OK-H and OK-O), rat, and human receptors, to isolate compounds. However, applicants' independent claims 40, 58, and 71 do not recite using a any particular PTH receptor. Rather, PTH receptors (or fragments thereof) isolated from any animal source (human or non-human) can be used in these methods. Applicants respectfully submit that they are entitled to pursue these generic claims, and that they should be

restricted to examination of claims reciting the use of specific PTH receptors only if their generic claims are found not to be allowable. Applicants submit that there would seem to be no undue burden on the Examiner to search the subject matter of all of the groups at the same time (particularly since all of these sequences have been examined and found novel in prior patents in this series). Therefore, applicants request that Groups I and IV to X be recombined into a single group.

III. Rejections under § 112, second paragraph

Claims 40, 42 and 43 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite due to applicants' use of the term "parathyroid hormone receptor." The Office Action states that the term is ambiguous and not defined in the specification. Applicants traverse this rejection because the term is art-recognized, and any skilled practitioner would have known what it meant at the time the priority application was filed, as well as now. Parathyroid hormone had been extensively studied in the prior art, of course, and its ability to bind to and activate an unidentified structure generically known as "parathyroid hormone receptor" was well known (see, e.g., the Lindall reference (U.S. Patent No. 4,508,828) cited by the Examiner in another context). Apparently, Lindall *et al.* understood what the term "parathyroid hormone receptor" meant back in 1983. Further, the term is amply described and defined throughout the instant specification, and is therefore unambiguous. For example, SEQ ID NOs: 18, 19, 20 and 21 are consistently referred to as "parathyroid hormone receptors" throughout the specification, e.g., at page 36, lines 18 to 27, and at page 8, lines 1 to 18. The functions and structure of PTH receptors in general are also thoroughly described in the specification, e.g., at page 16, lines 7 to 17, page 27, line 1, to page 30, line 9, and at page 33, line 28 to page 34, line 4. Further, applicants have provided in the specification a drawing that shows a predicted arrangement of extracellular, intracellular, and transmembrane domains of a PTH receptor, thus illustrating pictorially what a parathyroid hormone receptor looks like (see Fig. 21 and the specification at page 37, lines 14 to 16). Applicants therefore submit that the metes and bounds of the term are clear, and request that the present rejection be reconsidered and withdrawn.

Claims 42 and 43 were also rejected as allegedly indefinite due to applicants' use of the term "naturally occurring." Examiner Eyler indicated (during an interview on

September 18, 2002) that this term is now frowned upon by the Office due to the Office's adoption of a new policy specifically regarding the term. The Examiner explained that the Office believes the term is problematic under 35 U.S.C. § 112, second paragraph, because a skilled practitioner would allegedly not be able to tell the difference between a naturally occurring and non-naturally occurring product (in this case, a PTH receptor). Examiner Eyler further indicated that the rejection of claims 40, 42, and 43 under 35 U.S.C. § 112, first paragraph (discussed in further detail below), stems from this issue.

In the interest of moving this application toward allowance, applicants have amended claim 42 to recite "wherein the sequence of the polypeptide is identical to the sequence of a fragment of a naturally occurring parathyroid hormone receptor." Claim 43 has been amended similarly. Applicants have amended these claims to make it clear that the claim was not meant to be limited to fragments of proteins literally isolated from nature (i.e., non-recombinant proteins). As amended, the claim scope now clearly encompasses fragments of non-recombinant proteins as well as polypeptides that are produced recombinantly. "Naturally occurring" as used in claim 42 characterizes the sequence as one that is found in nature. Indeed, applicants obtained allowance of many other claims utilizing this term in patents related to the present application (see U.S. Patent Nos. 5,886,148, 5,840,853 (parent to the present application), and 5,494,806 (grandparent to the present application)). As stated in the Manual of Patent Examining Procedure (MPEP) at § 1701, a patent is presumed valid. Thus, applicants request that the present rejection be reconsidered and withdrawn.

IV. Rejection under 35 U.S.C. § 112, first paragraph

Claims 40, 42, and 43 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description. The Office Action states (at page 4):

> Claims encompass a polypeptide variant PTH receptor which is naturally occurring but not disclosed in the specification nor to one of skilled in the art. The essential feature of the invention is the methods of binding using the SEQ ID NO:21 PTH receptors. The claimed polypeptide variants encompass a large genus of receptors which are alleles or variants whose structure has yet to be identified from different species of animal because the structure of the newly identified naturally occurring receptor is not known. One of skilled in the art cannot envision the sequence which has not been identified. *University of*

> *California v. Eli Lilly and Co.* (CAFC) 43 USPQ2d 1398 held that a generic claim to human or mammalian when only the rat protein sequence was disclosed did not have written description in the specification.

As a preliminary matter, applicants disagree with the Office Action's assertion that "the essential feature of the invention is the method of binding using the using the SEQ ID NO:21 PTH receptors." Rather, an essential feature of claim 40 is the use of a polypeptide that comprises a PTH-binding fragment of any PTH receptor, not just the human PTH receptor set forth as SEQ ID NO:21. Applicants remind the examiner that they were the first to clone and sequence cDNAs encoding PTH receptors in general, including but not limited to the human cDNA. Thus, the invention is not limited to the human sequence.

As discussed above, Examiner Eyler indicated (during the interview on September 18, 2002) that the present rejection under 35 U.S.C. § 112, first paragraph, is related to the rejection of the claims under 35 U.S.C. § 112, second paragraph, for use of the term "naturally occurring." The Examiner explained that the Office now finds this terminology to be problematic under 35 U.S.C. § 112, first paragraph. To address the Office's concerns, applicants have amended claims 42 and 43 as described above, to clarify that the polypeptide includes an amino acid sequence identical to the sequence of a naturally occurring PTH receptor or a fragment thereof. The claims now unambiguously cover both polypeptides extracted from natural tissues and those produced by other means (e.g., recombinantly or by synthetic chemistry).

From the statement quoted above, applicants understand that the Office Action also rejects the claims as lacking written description because the term "parathyroid hormone receptor" encompasses a large genus of receptors having members that are allegedly not fully described in the specification. Applicants traverse this rejection because they satisfy the written description requirement for use of the full genus of PTH receptors through a description of a representative number of PTH receptor species, as well as by disclosure of relevant, identifying characteristics of the PTH receptors, e.g., structural and chemical properties (*see* the MPEP at §2163(II)(A)(3)(a)(ii)). According to the MPEP §2163 (II)(A)(3)(a)(ii):

> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to

> reflect the variation within the genus. On the other hand, there may be situations where one species adequately supports a genus.

Applicants submit that the PTH receptors described in the specification (e.g., by providing nucleic acid and amino acid sequences) are representative of the entire genus of PTH receptors, and that a sufficient variety of species is described to reflect the variation within the genus. Applicants have described the cloning and identification of not one, but four PTH receptors isolated from three distantly related mammals, including rat, opossum, and human. In the experiments disclosed and discussed at page 16, line 6 to page 32, line 28, applicants show that the sequences of the PTH receptors are highly conserved. The Examiner's attention is directed to Figures 5 and 6, which illustrate the point that the sequences of the rat, opossum, and human parathyroid hormone receptors are extremely well conserved. For example, the rat and opossum sequences are 78% identical at the amino acid level (see Figure 4); the opossum and human sequences are 81% identical; and the rat and human sequences are 91% identical. Applicants submit that this high level of identity over long stretches of amino acids is strong evidence that the sequence of the parathyroid hormone receptor is evolutionarily conserved to a high degree and, therefore, that there is relatively little variation within the genus of parathyroid hormone receptors. Thus, applicants submit that claims 40 and 43 fully comply with the written description requirement because they have described a number of PTH receptors which, as a group, are representative of the entire genus of PTH receptors and reflect the variations that may occur within this genus. Accordingly, applicants request that the present rejection be reconsidered and withdrawn.

Claims 40, 42, 43 and 57 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. Specifically, the Office Action states (at page 5):

> Claims encompass a polypeptide fragments and variants of PTH receptor which is six amino acids long. However, the specification does not teach how to use fragments and variants of PTH receptor which does not bind ligands.

Applicants respectfully traverse this rejection for the following reasons. First, applicants submit that it is well within a skilled practitioner's abilities to determine which fragments of a PTH receptor can bind to PTH, especially in view of the detailed information provided in the

specification. For example, the specification discloses the full nucleic acid and amino acid sequences of 4 different PTH receptors, and provides a figure illustrating a predicted arrangement of extracellular, intracellular, and transmembrane domains of a PTH receptor (see Fig. 21). Also disclosed at page 37 are the amino acid sequences of both the extracellular and intracellular domains of the rat bone PTH receptor (SEQ ID NOs:5 to 13). These domains were synthesized and purified by the applicants (see page 37, line 17, to page 38, line 3), and range in length from 10 to 25 amino acid residues. The specification also teaches that the sequences of PTH receptors are highly conserved, allowing data from PTH receptors described in the specification to be extrapolated to PTH receptors from other species (page 23, lines 25 to 30). Applicants submit that with such detailed information, a skilled practitioner would know the structure of any PTH receptor and could easily determine which fragments bind to PTH through routine and predictable experimentation.

Second, applicants traverse the present rejection because the language of claim 40 renders the rejection moot. Specifically, part (a)(ii) of claim 40 requires that the polypeptide be capable of binding to parathyroid hormone. Part (a) of amended claim 40 recites:

> (a) providing a recombinant polypeptide that: (i) comprises at least 6 amino acids and less than the complete amino acid sequence of a parathyroid hormone receptor, and (ii) binds to parathyroid hormone.

Applicants submit that (a)(ii) of claim 40 excludes polypeptides that are unable to bind parathyroid hormone. Thus, the Examiner's concern that "the claim encompasses a genus with a large number of species which are not functional" (Office Action at page 6) is unwarranted, and applicants request that the present rejection be reconsidered and withdrawn.

V. Rejection under 35 U.S.C. § 102

Claims 40, 42, 43 and 57 were rejected as allegedly anticipated by Lindall et al. (U.S. Patent No. 4,508,828). Lindall is a publication that describes methods for extracting, concentrating, and measuring parathyroid peptides in biological fluids (apparently they mean parathyroid hormone peptides: see, e.g., the term "PTH peptides" used frequently in Col. 3 and elsewhere throughout the reference).

As discussed during the interview, applicants have amended claim 40 to recite:

(a) providing a recombinant polypeptide that: (i) comprises at least 6 amino acids and less than the complete amino acid sequence of a parathyroid hormone receptor, and (ii) binds to parathyroid hormone.

This amendment is supported throughout the specification, e.g., at page 38, lines 5 to 10. There, the specification teaches that the polypeptides can be produced by expression from a recombinant nucleic acid using any appropriate expression system, supporting recitation of the term "recombinant."

Applicants submit that Lindall does not describe the use of recombinant polypeptide as required by amended claim 40. The methods described in Lindall involve assays that employ animal tissue, cultured animal cells, or tissue extracts containing PTH receptors (see Lindall at column 3, lines 21 to 24). The PTH receptors that are allegedly inherently taught in Lindall are receptors that are expressed naturally by cells that produce PTH receptors. The receptor described in Lindall cannot be considered "recombinant" because it was not produced by expression from a recombinant nucleic acid, nor would it be present in the same cellular milieu as a recombinant PTH receptor. Thus, Lindall does not anticipate amended claim 40 (or claims 42, 43, or 57, which depend therefrom) because Lindall does not describe all of the limitations recited by this claim. In view of the above, applicants respectfully request that the present rejection be withdrawn.

CONCLUSION

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made."

Applicants ask that all claims be allowed. Enclosed is a check for $520 for the Petition for Extension of Time fee (the fee for the first two months having been paid on October 9, 2002). Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 00786-071005.

Respectfully submitted,

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Version with Markings to Show Changes Made

In the Claims:

Claims 44 to 51 have been cancelled.

Claims 40, 42, 43, and 57 have been amended as follows:

40. (Amended) A method for identifying a compound that inhibits binding of a parathyroid hormone to a parathyroid hormone receptor by competitively [competes with a parathyroid hormone for] binding to the [a] parathyroid hormone receptor, the method comprising:

(a) providing a recombinant polypeptide that: (i) comprises at least 6 amino acids and less than the complete amino acid sequence of a parathyroid hormone receptor, and (ii) binds to parathyroid hormone;

(b) contacting the polypeptide with a parathyroid hormone in the presence of a candidate compound; and

(c) comparing the level of binding of the polypeptide to the parathyroid hormone in the presence of the candidate compound with the level of binding of the polypeptide to the parathyroid hormone in the absence of the candidate compound, wherein a lower level of binding in the presence of the candidate compound than in its absence indicates that the candidate compound competes with parathyroid hormone for binding to the receptor.

42. (Amended) The method of claim 40, wherein the sequence of the polypeptide is identical to the sequence of a fragment of a naturally occurring parathyroid hormone receptor.

43. (Amended) The method of claim 40, wherein [the]said sequence of the polypeptide is identical to the sequence of a fragment of a naturally occurring human parathyroid hormone receptor.

57. (Amended) The method of claim 40, wherein said [the] complete amino acid sequence of the parathyroid hormone receptor in (a)(i) consists of SEQ ID NO:21.